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PATENT APPLICATION Attorney Docket No. SCH01.NP001

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

#5a 10/20/00 JBray

In re the Application of:
Jay SCHNEIDER
Serial No.: 09/435,249 Art Unit: 1635
Filed: November 5, 1999 Examiner: Schmidt, M.

For: TREATMENT FOR PARKINSON'S DISEASE WITH OLIGONUCLEOTIDES

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION

Dear Sir:

This responds in full to the non-final Official Action mailed March 30, 2000 (Paper Number 2). This response is timely filed by virtue of the enclosed Petition for Extension of Time, extending the time for response through and including October 2, 2000, thereby extending by three months the shortened statutory time period in which to respond to the Official Action.

RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

In response to the "Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures", submitted herewith is a "Sequence Listing" in computer readable form, and paper copy of the sequence listing in accordance with the requirements of 37 CFR 1.821 - 1.825. A copy of the notice is enclosed.

PRELIMINARY AMENDMENT

Applicant respectfully requests entrance of the following Preliminary Amendment into the record of the above-captioned application.

In the Specification:

Following the abstract on Page 18, please insert the paper copy containing Sequence Nos. 1 - 6 that have been formatted in FastSeq Version 4.0 to conform with 37 C.F.R. 1.823.

STATEMENT PURSUANT TO 37 C.F.R. 1.821(f) and (g)

The undersigned hereby certifies in accordance with the requirements of 37 C.F.R. 1.821(f) and (g), that that the contents of the paper and computer-readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. §§ 1.821 - 1.825, respectively are the same. The undersigned hereby states that no new matter is introduced by this submission.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1 to 22 are currently pending in the present application. The Examiner has rejected claims 1 to 22 under 35 U. S. C. §112, first paragraph. The Examiner states:

"the specification, while being enabling for administration of specific antisense oligonucleotides for therapeutic purposes claimed, does not reasonably provide enablement for administration of any such antisense or triplex therapeutic molecule for the function claimed."

The Applicant respectfully submits that the rejection under 35 U. S. C. §112, first paragraph, is improper. While the specification provides administration of specific antisense oligonucleotides for therapeutic purposes, the claims to methods of treating Parkinson's disease via administration of a therapeutically effective amount of antisense or triplex oligonucleotide to regions of the brain for downregulation of GAD_{65} and/or GAD_{67} (claims 1-16); for the downregulation of glutamate receptors (claims 17-20); or for the downregulation of GABA receptors (claims 21-22) are enabled.

The Applicant clearly explains how to make the invention. MPEP §2164 defines enablement as:

"...the specification describe[s] how to make and how to use the invention. ...in such terms that one skilled in the art can make and use the claimed invention ... [and] to ensure that the invention is communicated to the interested public in a meaningful way. ...sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary."

The Applicant's invention relates to methods of treatment of Parkinson's disease in a mammal, wherein an oligonucleotide is delivered directly to a specific area of the brain, by direct injection into that specific region of the brain, for downregulation of the specific target, wherein the target is GAD_{65} and/or GAD_{67}, glutamate receptors, or GABA receptors The making of the oligonucleotides, although well known to those skilled in the art, is detailed on page 8, beginning on line 13. Further, on page 10, beginning on line 9, the Applicant details the induction of a Parkinson

disease model in rats. The induction of Parkinsonian symptoms in squirrel monkeys is also detailed, beginning on page 12, line 15. The Applicant defines the best mode of antisense treatment (beginning on page 10, line 30), and further details the efficacy of the therapeutic methods beginning on page 13, line 13.

The Applicant respectfully submits that the administration of any oligonucleotide to the target nucleic acid will inhibit, to varying efficiencies, the expression of the target GAD_{65} and/or GAD_{67}, glutamate receptors, or GABA receptor nucleic acids. Specific decisions by the Federal Circuit are herein disclosed in support thereof.

The Applicant respectfully submits that specific examples of oligonucleotide inhibition of GAD_{65} and/or GAD_{67} enable the invention as claimed. Oligonucleotides targeted to regions between the 5' untranslated region, through the coding region, to the 3' untranslated region have been shown to have some efficacy. The efficacy of different target sites will vary, therefore some experimentation may be necessary in order to define the most efficacious target site for a particular gene. The current application serves as a guide to those skilled in the art, allowing them to practice the invention as claimed.

The Examiner states:

"there is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. ... Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms."

The Applicant respectfully submits that the oligonucleotides were successfully delivered to their target site. The penetration of the oligonucleotide into the cell, the stability of the oligonucleotide and its binding to the target site are supported by the efficacy (detailed on pages 13-14 of the present application) of the oligonucleotide therapeutics of the present invention.

I. Administration of "any such oligonucleotide to the target genes *in vivo*" is enabled.

The Examiner states:

"the specification as filed teaches success with administration of SEQ ID Nos. 1-6. However, such application would not be expected to correlate with administration of any such oligonucleotide to the target genes *in vivo* as broadly claimed."

There is a wide range of possible target sites on the gene of interest, as described *infra* in Section I.C., each of these will have some effect on the expression of that gene. In order to determine the most efficacious target site, some experimentation may be necessary. This is a well-known and common practice to those skilled in the art of antisense technology. The Applicant respectfully questions the Examiners view and presents publication references that exemplify this, as well as MPEP rules and case law decisions, that support the practice of experimentation by those skilled in the art and that this experimentation is not "undue" experimentation.

A. Non-inclusion of Limitations, Federal Circuit Decisions

While the results detailed in the current application describe the use of specific oligonucleotide sequences in the treatment of Parkinson's disease, the level of ordinary skill in the art is such that some experimentation may be necessary in order to practice the claimed invention. The Federal Circuit decision of *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510,1513 (Fed. Cir. 1993) states:

"the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'.

The court decision of *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) states:

"not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted."

Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims (see MPEP §2164.08).

In *In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970) the Federal Circuit stated:

"How a teaching is set forth, by specific example or broad terminology, is not important .... Claims are not rejected as broader then the enabling disclosure under 35 U.S.C. §112 for non-inclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art..."

Further, in *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721, F. 2d 1540, 1558, 220 USPQ 303, 316-17 (Fed. Cir. 1983) and *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977) the court states:

"One does not look to the claims but to the specification to find out how to practice the claimed invention."

In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:

[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Further, the MPEP §2164.08 clearly states:

"...limitations and examples in the specification do not generally limit what is covered by the claims."

B. Specific Examples Enable Claims

The Applicant does not detail the efficacy of all the oligonucleotide sequences that can be used to downregulate GAD_{65} and/or GAD_{67}, glutamate receptors or GABA receptors. As discussed *supra* the making and using of specific oligonucleotides is disclosed in the current application on pages 10 through 13. In more than one decision, *supra*, the case law has clearly found that as long as the specification teaches those skilled in the art everything necessary to practice the

invention, what is well-known is best omitted. The specific examples of oligonucleotides disclosed were designed to target the region surrounding the translation initiation codon. This region is known to be a sensitive target for hybridization, as it must be accessible for binding to the ribosome for translation of the RNA into protein. The efficacy of these antisense oligonucleotide examples are detailed, beginning on page 13, line 13. The specification of the current application enables those skilled in the art to practice the invention as claimed, as noted *supra* in the referenced MPEP sections §2164 and §2164.08.

C. Efficacy of Antisense Target Sites from 5' to 3' Untranslated Regions

While some amount of experimentation may be required to determine the efficacy of an oligonucleotide sequence, this is not "undue experimentation". Analysis of oligonucleotide efficacy is well known and common to those skilled in the art, as exemplified by methods published to facilitate the selection of the optimal oligonucleotide target site. For a computational approach to predicting oligonucleotide efficacy the Examiner is referred to Stull, R.A., et al., *Nucleic Acids Research* 20: 3501-3508, 1992. For a high throughput assay in which to determine oligonucleotide efficacy, the Examiner is further referred to Stull, R.A., et al., *Antisense Nucleic Acid Drug Development* 6: 221-228, 1996.

The Examiner refers to the success with the administration of SEQ ID Nos. 1-6, and further states:

"such application would not be expected to correlate with administration of any such oligonucleotide to the target genes *in vivo* as broadly claimed."

Experimentation to locate the best oligonucleotide target site is a well-known practice to those skilled in the art. As discussed *infra*, as well as in the references provided, oligonucleotides targeted to regions from the 5' untranslated region, through the coding region, to the 3' untranslated region, will inhibit, to varying extents, the target gene expression. To locate the most efficacious target site may require some experimentation. This is not undue experimentation, as the Examiner has suggested, it is well-known and a common practice to those skilled in the art of antisense technology.

Antisense oligonucleotides targeted to regions from the 5' untranslated region to the 3' untranslated region of the target RNA transcript will inhibit mRNA expression to varying degrees (Bacon, T.A. and Wickstrom, E., *Oncogene Research* 6: 13-19, 1991; Bennett, C.F., et al, "Pharmacology of Antisense Therapeutic Agents". *Methods in Molecular Medicine: Antisense Therapeutics* (Agrawal, S, ed.), Humana Press, Totowa, New Jersey, pp. 13-46, 1996). As disclosed by Bacon: " ...effectiveness of a particular oligonucleotide might correlate with the extent of secondary structure at each corresponding mRNA target, the number of G-C base pairs in the hybrid, ...[the] varying efficiencies of cellular uptake, transport, or degradation for oligonucleotides of differing sequences."

D. The Application is a Guide to those Skilled in the Art

MPEP §2164.08(b) states:

"The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled."

As stated in Section II.C. *supra*, oligonucleotides targeted to regions between the 5' untranslated region, through the coding region, to the 3' untranslated region of the target nucleic acid will have some effect on gene expression. One skilled in the art is able to determine which oligonucleotides would be operative with a standard amount of experimentation that is normally employed in determining the efficacy of any antisense and triplex oligonucleotide. While some oligonucleotide sequences will be more effective in downregulation of the target gene then others, this is not considered a §112 non-enablement. As stated in MPEP §2164.08(b):

"...claims reading on ...inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments...:"

On page 8, beginning on line 15, the specification clearly defines oligonucleotide sequences which are operative in downregulating their target nucleic acids. The efficacy of downregulation of these oligonucleotides are fully described on page 13, line 13 through page 14, line 11. Specifically, the Examiner is referred to Figure 4, wherein the statistical significance of the therapeutic efficacy is shown.

In re Brandstadter, 484 F.2d 1395, 1406-07, 179 OSPQ 286, 294 (CCPA 1973) states:

"...[those] skilled in the art [should be able]... to make and use [the] claimed invention using the application as a guide." "The evidence provided by the application need not be conclusive but merely convincing to one skilled in the art."

The Applicant successfully treats both rats and squirrel monkeys with antisense oligonucleotide. The data presented are convincing of the efficacy of treating Parkinson's disease with antisense oligonucleotide targeted to GAD_{65} or GAD_{67} (the Examiner is referred to Figures 4 through 7). The success with the specific oligonucleotides disclosed allows for there to be a reasonable belief that other sequences targeted to GAD_{65}, GAD_{67}, glutamate receptors or GABA receptors will also downregulate their specific target nucleic acids. MPEP §2164.02 states:

"...applicant need not describe all actual embodiments."

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970):

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then enablement requirement of 35 U.S.C. §112 is satisfied."

The Applicant has disclosed a method for making and using specific sequences of oligonucleotides for the treatment of Parkinson's disease. The successful downregulation of target nucleic acid by the oligonucleotide enables those skilled in the art to practice the claimed invention with other embodiments, more specifically with other oligonucleotide sequences targeted to GAD_{65}, GAD_{67}, glutamate receptor or GABA receptor nucleic acids.

II. Antisense Therapeutics: penetration, stability and binding to the target site

The Examiner states:

"The factors considered barriers to successful delivery of antisense to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding."

The Applicant respectfully disagrees, the rejection based on these "barriers of delivery" are improper. The Applicant successfully showed a reduction in the target nucleic acids when animals were treated with antisense oligonucleotide (see page 13). In addition, monkeys treated with antisense showed an increased spontaneous activity, while those that were treated with missense oligonucleotides did not. The downregulation of GAD following oligonucleotide delivery reveals that the oligonucleotides successfully reached their target sites. This success with *in vivo* antisense therapeutics is testimony to their efficacy. The Applicant refers to Akhtar and Agrawal "In Vivo Studies with Antisense Oligonucleotides" in *Trends in Pharmacol. Sciences*, 18: 12-18 (1997) wherein the authors disclose many specific examples of *in vivo* efficacy in animal models, as well as ongoing human clinical trials with oligonucleotides.

The Applicant respectfully questions the Examiners view that oligonucleotides are unable to "successful[ly] ... [achieve] penetration ...[into] target cells ...[in order] to find and bind the target site...." The Applicant achieves adequate tissue distribution, cellular uptake and nuclear localization for hybridization to the target nucleic acid to occur, thereby resulting in downregulation of the target gene expression.

A. Tissue Distribution of Oligonucleotides

A fairly detailed understanding of the pharmacokinetic properties of oligonucleotide therapeutics has been published by a number of groups. Briefly, the distribution of oligonucleotides to the tissues occurs very rapidly, plasma half-lives are less than one hour. In addition, direct injection into the brain results in a strong uptake immediately surrounding the injection site. The Examiner is referred to the following references for a fully detailed description of the mechanisms of organ uptake and cellular localization: Cossum, P.A., et al., *J. Pharmacol. Exp. Ther.* 267: 1181-1190, 1993; Cossum, P.A., et al., *J. Pharmacol. Exp. Ther.* 269: 89-94, 1994; Agrawal, S., et al., *Proc. Natl. Acad. Sci.*, 88: 7595-7599, 1991; Temsamani, J., et al., *Antisense Res. Dev.* 3: 277-284, 1993; Sands, H., et al.,

Mol. Pharmacol. 45: 932-943, 1994 and Saijo, Y., et al., *Oncol. Res.* 6: 243-249, 1994.

The Examiner further states:

"There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: ... (3) the ability to find and bind the target site and simultaneously avoid non-specific binding."

The Applicant discloses that the best mode of delivery to the target tissue is by direct injection into the brain (page 4, line 4). Direct injection into the brain results in a strong uptake by cells at the injection site, for pharmacokinetic details following intracerebral injection the Examiner is referred to Brysch, et al. ("Antisense-Mediated Inhibition of Protein Synthesis" *Methods in Molecular Medicine: Antisense Therapeutics* (Agrawal, S, ed.), Humana Press, Totowa, New Jersey, pp. 166 and 175-176, 1996).

The Examiner also states:

"Specifically the specification does not teach ... (2) effective delivery to the whole organism and specificity to the target tissues..."

The Applicant delivers the oligonucleotide directly to the target site by direct injection of the oligonucleotide into the specific brain region where the target cells are located. This negates having to deliver oligonucleotide to the whole organism, thereby circumventing any sequesterization by the liver and kidney, with their subsequent clearance of oligonucleotide.

B. Cellular Uptake of Oligonucleotides

The Examiner states:

"The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus...."

Following localization to the target tissue, which in the present application is by direct injection at the target site, the nucleic acid is taken up by the cells. To be effective, intact oligonucleotides must reach the cytoplasm and then the nucleus.

Nuclear pores do not represent a barrier, as direct injection into the cytoplasm will result in nuclear localization.

Receptors or channels for nucleic acid uptake have been identified on a variety of cells. It is common knowledge to those skilled in the art that cellular uptake of nucleic acids is by endocytosis (Loke, S.L., et al., "Characterization of Oligonucleotide Transport into Living Cells", *Proc. Natl. Acad. Sci. USA* 86: 3474-3478, 1989). The most efficient mechanism of vesicular endocytotic uptake is by receptor-mediated endocytosis. For example, de Diesbach, et al. (*Nucleic Acids Res.* 28: 868-874, 2000 and the references contained therein), identified a new membrane protein that acts as an oligonucleotide receptor on liver cells. Further, Hanss, et al. (*Proc. Natl. Acad. Sci. USA* , 95: 1921-1926, 1998) have identified a cell membrane nucleic acid channel on kidney cells that conducts nucleic acids into the cell. In addition, Benimetskaya, et al. (*Nature Medicine,* 3: 414-420, 1997) have identified a cell-surface receptor on white blood cells for oligonucleotides that mediates their internalization. Specific receptors for oligonucleotide uptake into mammalian cells is well known in the art, as further exemplified by Yakubov, et al. in 1989 (*Proc. Natl. Acad. Sci. USA,* 86: 6454-6458). This publication also reports the endocytic uptake of oligonucleotides, as well as oligonucleotide stability in both the cytoplasm and nuclei. These results, by various investigators dating back to at least 1989, reveal that it is well known in the art that uptake into the cells is known, and does occur such that oligonucleotides are stable and reach their target nucleic acid, with the subsequent inhibition of gene expression.

The Examiner further states:

"Specifically the specification does not teach ... (4) entry of molecule[s] into [the] cell and [their] effective action therein marked by visualization of the desired treatment effects for the scope of possible target regions."

The "effective action" is the downregulation of the target nucleic acid, in the specific examples disclosed these target nucleic acids are GAD_{65} and GAD_{67}. As described *supra* the Applicant successfully showed the efficacy of the treatment in rats on page 13, beginning on line 13, and in squirrel monkeys on page 14, lines 7 through 11. This therapeutic response to antisense treatment is "visualization of the desired treatment effects", since the objective is to treat Parkinson's disease, the

treatment being correction of the impaired neurochemical circuitry. The correction of the impaired neurochemical circuitry is visualized by correction of impaired movement, a characteristic symptom of Parkinson's disease.

C. Nuclear Localization and Hybridization to Target Nucleic Acid

The Examiner states:

"The factors considered barriers to successful delivery of antisense to the organism are: ... (3) the ability to find and bind the target site and simultaneously avoid non-specific binding."

As stated *supra* in Section II. A., direct injection of the oligonucleotide into the region of the brain where GAD overexpression is to be regulated negates issues of tissue distribution, since direct injection to the delivery site allows for a rapid uptake into cells at that site. Once inside the cytoplasm (see Section II.B., *supra*) the oligonucleotide must enter the nucleus and hybridize to the target nucleic acid. The mechanism of action of nuclear entry has also been studied and it is generally believed that nucleic acids enter, and exit, the nucleus via nuclear pores. The "ability to find and bind the target site and simultaneously avoid non-specific binding", that is to hybridize to the target nucleic acid within the nucleus, is a prerequisite for downregulation of the target nucleic acid. As discussed *supra* the efficacy of downregulation is detailed in the current application on pages 10 through 13. The Examiner is referred to Politz, et al., *Proc. Natl. Acad. Sci. USA*, 95, 6043-6048, 1998 and also to Politz, et al., *Nucleic Acids Res.*, 23: 4946-4953, 1995 for a detailed biochemical disclosure on the intranuclear hybridization of oligonucleotide to target nucleic acid.

III. Efficacy of Antisense Therapeutics

The Examiner states:

"One of skill in the art would not accept on its face the successful delivery of any antisense molecule *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art."

As described *supra*, as well as in the references disclosed herein, those skilled in the art acknowledge that some oligonucleotides targeted to a gene are more effective than are others targeted to that same nucleic acid. While there are some differences in the effectiveness of the various oligonucleotide sequences targeted to the same nucleic acid, some antisense activity is detected at each target site (for example see Bacon, T.A. and Wickstrom, E., *Oncogene Research* 6: 13-19, 1991 and Bennett, C.F., et al, "Pharmacology of Antisense Therapeutic Agents". *Methods in Molecular Medicine: Antisense Therapeutics* (Agrawal, S, ed.), Humana Press, Totowa, New Jersey, pp. 13-46, 1996).

A. Dosage and Toxicity

The Examiner also states:

"Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach ... (3) dosage and toxicity...".

The dosage of antisense for the rat experiments is clearly defined on page 11, lines 4-5 and on page 12, line 14. The dosage of antisense for the squirrel monkey experiments is clearly defined on page 12, line 31 to page 13, line 2. As occurs in any therapeutic protocol, specific dosage is to be determined on an individual basis with administration dependent on the condition of the patient and the response of that patient to the treatment. Since this application discloses that the best mode of delivery is by direct injection into the brain, there is no concern for systemic toxicity, since the oligonucleotides remain in the brain tissue. They do not cross the blood-brain barrier. Therapeutic concentrations are maintained within the cerebral spinal fluid compartment with subsequent extensive penetration into the brain tissue without gross toxicity. See Whitesell, et al. for a complete description of the stability, clearance and disposition of intracerebral administration of oligonucleotides (*Proc. Natl. Acad. Sci. USA* 90: 4665-4669, 1993).

The Applicants believe that claims 1-22 are enabled, as defined by the first paragraph of 35 U. S.C. §112, and should now be examined on the merits. Prompt consideration and allowance of claims 1-22 are earnestly solicited.

Should the Examiner determine that any further action is necessary to place this application into even better form, she is encouraged to telephone the Applicants undersigned representative at the number listed below.

Respectfully submitted,

SCHNEIDER, Jay S.

9/29/00
Date

BY: Janet B. Smith

Janet B. Smith, Ph.D.
Patent Agent
Registration No. 45,461
Thomas Jefferson University
Office of University Counsel
1020 Walnut Street – Suite 626
Philadelphia, PA 19107
Phone: (215) 503-2368
Fax: (215) 923-3613

Enclosures
(copies of references cited herein)